Tetrahedron Letters,Vol.25,No.52,pp 6011-6014,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

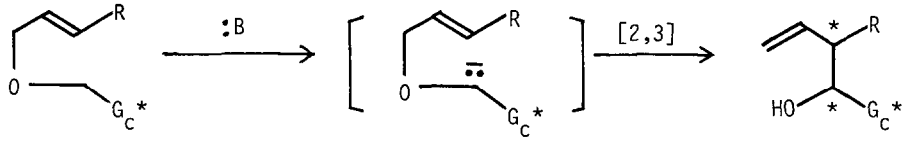
ASYMMETRIC [2,3]WITTIG SIGMATROPIC REARRANGEMENT INVOLVING A CHIRAL AZAENOLATE AS THE MIGRATING TERMINUS. A SIMPLE SYNTHESIS OF (+)-VERRUCARINOLACTONE

Kōichi Mikami, Katsuhiko Fujimoto, Takashi Kasuga, and Takeshi Nakai*

Department of Chemical Technology, Tokyo Institute of Technology,
Meguro-ku, Tokyo 152, Japan

SUMMARY: The diastereo- and/or enantioselection are described in the title rearrangement of the chiral 2-(2-alkenyloxy)methyl 2-oxazolines which eventually provides optically active α-hydroxy γ,δ-unsaturated esters and (+)-verrucarinolactone.

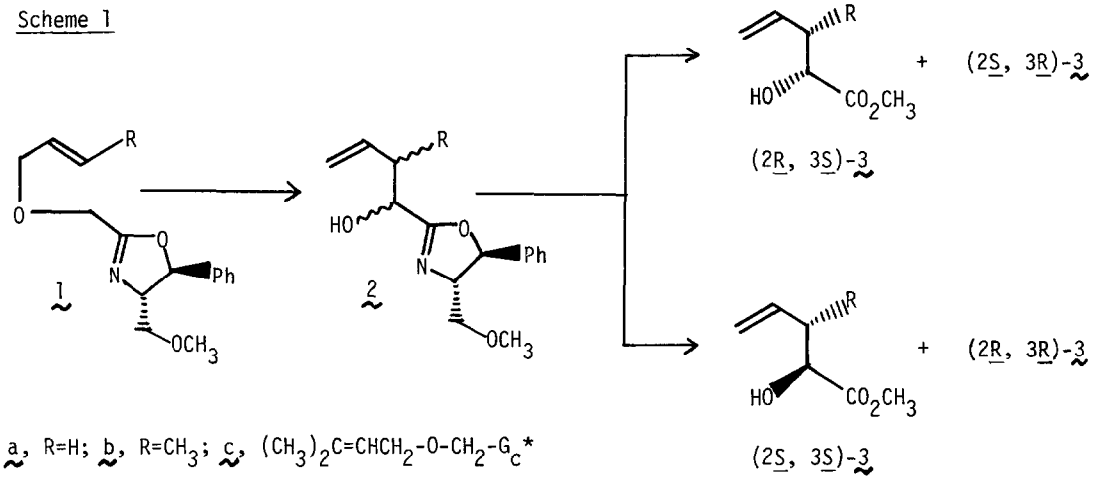
The control of both diastereo- and enantioselection during carbon-carbon bond formations is of great importance in synthesis. Recently remarkable success has been reached in aldol-type reactions using properly designed chiral enolates.[1] In a continuing effort to develop the [2,3]Wittig sigmatropic rearrangement into a new, general strategy for acyclic stereocontrol,[2] we were interested in the asymmetric [2,3]Wittig process which involved a chiral enolate as the migrating terminus (eq 1). We now report the first example of this type of asymmetric sigmatropic rearrangement that exhibits a high degree of both diastereo- and enantioselection.



(1)

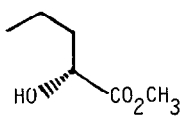
For this study was selected Meyers' chiral oxazoline ring[3] as the key chiral auxiliary (G_c*). Thus, we studied the [2,3]Wittig process of the three chiral oxazolines (1a-c),[4] which eventually afforded the chiral α-hydroxy esters (3) (Scheme 1). The rearrangement was carried out by using butyllithium or lithium diisopropylamide (LDA) as the base in THF at -85 °C, stirring for 3-5 h, and quenching with brine. Usual workup afforded an essentially quantitative yield of the rearranged product (2) which was converted to the hydroxy ester (3) via hydrolysis (3N H_2SO_4) followed by treatment with diazomethane. The three-step sequence from 1 was carried out without purification of intermediates. Table 1 summarizes the results.

Scheme 1

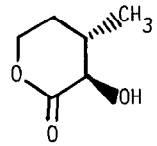


a, R=H; b, R=CH_3; c, $(CH_3)_2C=CHCH_2-O-CH_2-G_c$*

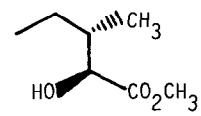
The assignment of the absolute configuration to the hydroxy esters 3 deserves comments. Ester 3a (entry 1) was hydrogenated to (-)-4 which was correlated to (-)-(R)-4 ($[\alpha]_D^{20}$ -12.5° ($CHCl_3$)) derived from D-norvaline via nitrous acid oxidation. In order to assign the absolute configuration to erythro-3b (major diastereomer), 3b (entry 3) was converted to verrucarinolactone (5) according to Roush's four-step procedure.[5] Recrystallization from ether gave stereochemically pure (2R, 3S)-5 (mp 103-104 °C [lit.,[6a] 103 °C]; $[\alpha]_D^{16}$ +13.8° (c 0.69, $CHCl_3$)), as judged from the highest literature value ($[\alpha]_D^{23}$ -10.4° ($CHCl_3$)) reported for (2S, 3R)-5.[6] On the other hand, threo-3b (minor diastereomer) was separated from the diastereomixture (entry 4) by preparative GLC and hydrogenated to (+)-6 which was correlated to (+)-(2S, 3S)-6 ($[\alpha]_D^{19}$ +29.3°($CHCl_3$)) prepared from L-isoleucine via nitrous acid oxidation.



(R)-(-)-4



(2R, 3S)-(+)-5



(2S, 3S)-(+)-6

Several significant trends are evident from the data in Table 1. (1) Butyllithium is superior to LDA as the base. (2) The present rearrangement exhibits a preference for the (R)-configuration at C-2 of 3 in general, the degree depending markedly on the methyl-substitution pattern on the allylic moiety. (3) Particularly noteworthy is the rearrangement of 1b (entry 3) which provides a dramatically enhanced enantioselectivity (78% ee) along with a high erythro-

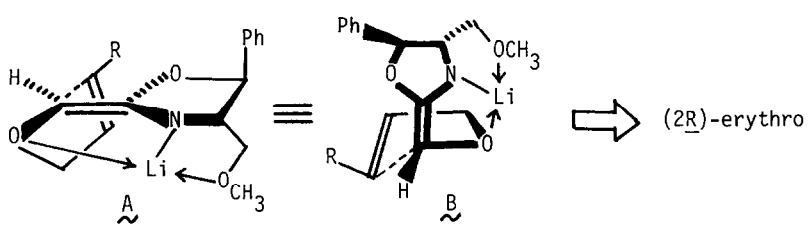
Table 1. The Chiral α-Hydroxy Esters (3) via Rearrangement of 1

Entry	Substrate	Base	Erythro : Threo[a]	% ee[b]	Configuration[c]
1	1a	n-BuLi		38[d]	R
2	1a	LDA		14[d]	R
3	1b (93% E)	n-BuLi	90 : 10	Erythro 78 Threo 8	2R, 3S 2S, 3S
4	1b (93% E)	LDA	84 : 16	Erythro 64 Threo 28	2R, 3S 2S, 3S
5	1c	n-BuLi		75	(R)[e]

a: Determined by GLC and NMR assays as described in ref 2c. b: Determined by NMR analysis using (+)-Eu(DPPM)$_3$ as the chiral shift reagent which was provided by Prof. N. Ishikawa: cf. H. Kawa, et al., *Chem. Lett.*, 1982, 153. The NMR analysis of 3b was done without separation of the diastereomers; the CH_3O-signal was separated to four signals. c: Unless specifically noted in the text, the configuration was assigned by similarity in shifts using the chiral shift reagent. d: Refers to the % ee for the α-methoxy ester of 3a. e: Assigned only by assuming the same sense of enantioselection as observed for 1a.

selectivity (90%). (4) The rearrangement of 1c also shows a comparably high level of enantioselection. Thus, these findings reveal that the added methyl group(s) on the allylic moiety appears to exert a great influence in dictating the enantioselectivity.

Although these trends have no definitive explanations owing to the complexities of this process, the observed sense of enantioselection is reasonably interpreted as the result that the enolization leads to the metal-chelated (Z)-enolate[7] (see formula A depicted below) which undergoes the [2,3]-shift preferentially from the bottomside (re-face). The great enhancement in % ee by changing the migrating group from allyl (1a) to (E)-crotyl (1b) (or prenyl (1c)) might be rationalized in terms of a steric interaction between the crotyl-methyl and the phenyl which substantially depresses occurrence of the topside (si-face) rearrangement. Thus, both the high erythro- and enantioselectivity observed for 1b can be visualized by the transition state B (R=CH_3)[8] with the oxazoline ring at the pseudo-axial position and the methoxymethyl



group at the re-face. Further efforts are in progress to probe this interesting process and to examine [2,3]Wittig rearrangements involving different chiral enolates.

Acknowledgments: This research was generously supported by the Kurata Foundation and the Grant-in-Aid for Special Project Research from the Ministry of Education, Japan.

References and Notes

1. Recent reviews: D. A. Evans, J. V. Nelson, and T. R. Taber, "Topics in Stereochemistry", Vol. 13, John Wiley, 1982, p.1; C. H. Heathcock, "Asymmetric Synthesis", Vol. 3B, Academic Press, 1984, p.111.

2. (a) Review: T. Nakai, K. Mikami, and N. Sayo, *J. Synth. Org. Chem.,Jpn.*,41, 100(1983);(b) For self-immolative asymmetric versions, see: N. Sayo, K. Azuma, K. Mikami, and T. Nakai, *Tetrahedron Lett.*, 25, 565 (1984); N. Sayo, E. Kitahara, and T. Nakai, *Chem. Lett.*, 1984, 259; (c) For the [2,3]Wittig process involving achiral azaenolates derived from Meyers' heterocycles, see: K. Mikami, K. Fujimoto, and T. Nakai, *Tetrahedron Lett.*, 24, 513 (1983).

3. Reviews: A. I. Meyers, *Acc. Chem. Res.*, 11, 375 (1978);*Idem, Pure Appl. Chem.*, 51, 1255 (1979).

4. Substrates 1 were prepared in 52-70% overall yields via reaction of the potassium salt of an allylic alcohol with the 2-chloromethyl-4-hydroxymethyl-2-oxazoline (mp 89-90 °C), prepared from commercial (1S, 2S)-2-amino-1-phenyl-1,3-propanediol and the imino ether of chloroacetonitrile, followed by methylation (CH_3I/KH) of the 4-hydroxymethyl moiety.

5. W. R. Roush, T. A. Blizzard, and F. Z. Basha, *Tetrahedron Lett.*, 23, 233 (1982). The sequence involves silylation (t-BuMe_2SiCl/imidazole), hydroboration/oxidation (disiamylborane→H_2O_2/NaOH), and desilylation (HF, CH_3CN).

6. For synthesis of (-)-5, see:(a) W. C. Still and H. Ohmizu, *J. Org. Chem.*, 46, 5242 (1981); (b) K. Tomioka, F. Sato, and K. Koga,*Heterocycles*, 17, 311 (1982);(c) B. M. Trost and P. G. McDougal, *Tetrahedron Lett.*, 23, 5497 (1982);(d) Y. Yamamoto, N. Maeda, and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 1983, 774.

7. Recently it has vigorously been established that enolization of α-alkoxy esters with LDA exclusively leads to the (Z)-enolates via chelation control by the alkoxy group: S. D. Burke, W. F. Fobare, and G. J. Pacofsky, *J. Org. Chem.*, 48, 5221 (1983); J. Kallmerten and T. J. Gould, *Tetrahedron Lett.*, 24, 5177 (1983).

8. Other possible transition states with the heterocycle at the pseudo-equatorial position which lead to threo-3 is sterically disfavored due to the large pseudo-gauche repulsion between R and the heterocycle. For a general discussion of the transition-state model for [2,3]Wittig process, see: K. Mikami, Y. Kimura, N. Kishi, and T. Nakai, *J. Org. Chem.*, 48, 279 (1983). It should be noted here that the present [2,3]Wittig variant is exceptional in terms of the sense of diastereoselection, since the [2,3]-process of (E)-crotyl ethers in general exhibits threo-selection.

(Received in Japan 4 September 1984)